

Monitoring and Management of Immune-Related Adverse Events Associated With Programmed Cell Death Protein-1 Axis Inhibitors in Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Lung cancer • Immune-related adverse events • Programmed cell death protein-1 • Programmed death ligand-1 • Immunotherapy • Toxicities

ABSTRACT

Monoclonal antibodies targeting programmed cell death protein-1 (PD-1) represent a new treatment paradigm in non-small cell lung cancer. Three phase III trials have demonstrated a survival benefit and improved tolerability of nivolumab and pembrolizumab when compared with standard second-line chemotherapy.

Nevertheless, the adverse events associated with PD-1 inhibitors are unique; early recognition and treatment are essential. This review summarizes the required monitoring and appropriate management of immune-related adverse events in lung cancer patients receiving these agents. *The Oncologist* 2017;22:70–80

Implications for Practice: The potential adverse events of immune checkpoint inhibitors differ from conventional chemotherapy and can require a multidisciplinary approach. Continued education is important for all physicians to ensure optimal care for patients.

INTRODUCTION

Monoclonal antibodies against programmed cell death protein-1 (PD-1) have recently received regulatory approval and are now incorporated as a standard option in guidelines for treatment of metastatic non-small cell lung cancer (NSCLC) [1]. Additionally, agents targeting programmed death ligand-1 (PD-L1) are showing promise in clinical trials. Although these are generally well tolerated, they are associated with novel immune-mediated toxicities, called immune-related adverse events (irAEs) [2]. In a similar paradigm of the management of patients treated with targeted therapies [3], immune checkpoint inhibitors (ICPIs) represent a new and distinct class of treatment for NSCLC, and therefore clinicians and patients may benefit from guidelines for monitoring and management of irAEs. This review summarizes the toxicity data in NSCLC, primarily focusing on results of randomized phase III studies, which are similar to previously reported phase I and II data.

OVERVIEW OF APPROVED PD-1 INHIBITORS

PD-1 is expressed on a high proportion of tumor-infiltrating lymphocytes, and binding to its ligands (PD-L1 and PD-L2) promotes tumor immune escape [4]. PD-L1 can be found on a spectrum of cells including endothelial and epithelial cells together with T and B cells, mast and dendritic cells; PD-L2

expression is more limited and includes dendritic, mast cells and macrophages. A number of solid tumors upregulate PD-L1, avoiding immune surveillance; this is known to confer an inferior prognosis in NSCLC [5]. Nivolumab and pembrolizumab are IgG4 monoclonal antibodies targeting PD-1, with data supporting their efficacy in treating NSCLC.

A phase III study in patients with advanced, previously treated squamous-cell NSCLC (Checkmate 017) [6] compared nivolumab 3 mg/kg every 2 weeks with docetaxel chemotherapy and demonstrated superior overall survival (OS) (median 9.2 vs. 6.0 months, hazard ratio [HR] 0.59, $p < .001$), response rate (RR) (20% vs. 9%, $p = .008$), and progression-free survival (median 3.5 vs. 2.8 months, HR 0.62, $p < .001$), regardless of PD-L1 expression level in the tumor. This trial led to U.S. Food and Drug Administration (FDA) approval of nivolumab in March 2015 for patients with metastatic squamous NSCLC with progression during or after platinum-based chemotherapy. Another phase III study with the same design in nonsquamous NSCLC (Checkmate 057) [7] also confirmed superiority of nivolumab over docetaxel in terms of OS (median 12.2 vs. 9.4 months, HR 0.73, $p = .002$) and RR (19% vs. 12%, $p = .02$). Although the benefit of nivolumab was observed in the overall population, it appeared to be greater among patients whose

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tumors expressed PD-L1. Interestingly, in a subgroup analysis, there was no survival benefit seen in never-smokers and patients with *EGFR* mutant tumors. On the basis of these data, the FDA extended the approval to all patients with NSCLC who progressed on or after platinum-based doublet. On March 1, 2016, Health Canada also approved nivolumab for metastatic NSCLC, as second-line therapy or beyond.

The phase II/III Keynote 010 trial [8] compared two doses of pembrolizumab, 2 mg/kg and 10 mg/kg every 3 weeks, with docetaxel in patients with previously treated, PD-L1-positive, advanced NSCLC. Survival was significantly longer in patients receiving either dose of pembrolizumab (HR 0.71, $p = .0008$, for 2 mg/kg and HR 0.61, $p < .001$, for 10 mg/kg). The FDA subsequently approved pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 with disease progression on or after platinum-containing chemotherapy.

In all of these trials, grade 3–5 treatment-related adverse events (AEs) were less common with immunotherapy than with docetaxel. PD-1 inhibitors are now incorporated in National Comprehensive Cancer Network guidelines [1] as the preferred choice for second-line therapy as a category 1 recommendation, on the basis of the results of the above studies.

OVERVIEW OF ADVERSE EFFECTS

The mechanisms of immune toxicities are not fully understood. The PD-1/PD-L1 pathway is important in immune homeostasis and suppression of T-cell activity against self-antigens [9]. By interrupting this inhibitory pathway, stimulation and proliferation of T cells occurs, presumably allowing for T-cell attack on normal tissue as well as tumor cells, leading to the development of autoimmune events [10].

In the three phase III trials described above, treatment-related AEs of any grade occurred in up to 69% of patients. Severe AEs of grade 3 or higher (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 4.0) were reported in 7%–13% of patients [6–8]. An awareness of irAEs and the risk factors associated with these is imperative prior to commencement of therapy. Patients with a personal history of autoimmune disease have been excluded from clinical trials because there remains concern regarding exacerbations, which have been reported and demonstrated preclinically [11–14]. Case reports and retrospective small series suggest that treatment with ICPIs may be feasible under careful surveillance with manageable toxicities [14–18]. If short courses of corticosteroids have been prescribed, these should be completed, or if required, patients should not be taking more than the physiologic equivalent of 10 mg prednisone daily. The impact of pre-existing steroid use or immunosuppressants and long-term efficacy of ICPIs is not known. Ipilimumab, a cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) inhibitor, has been administered successfully to solid organ transplant patients who developed melanoma several years later [19–21]. Transplant rejection has also been documented [22]; therefore the role of ICPIs in this cohort of patients is not yet known. A history of previous or chronic infections is important to establish: chronic hepatitis B or C infections as well as HIV infection have been exclusion factors in lung cancer trials of immunotherapy to date. Early phase II data and case reports,

however, suggest durable responses and a manageable safety profile in patients with controlled hepatitis B or C and hepatocellular carcinoma. [23, 24] This cohort of patients is unlikely to be excluded from immunotherapy in the future.

In Table 1, we describe the AEs most frequently seen in phase III studies. The majority of symptoms are mild and can be managed conservatively. Fatigue and asthenia are the most common AEs. It is important to exclude the presence of underlying endocrinopathies such as hypothyroidism and adrenal insufficiency, as discussed in the section Endocrine Disorders, below. Infusion-related reactions do not appear common with PD-1 inhibitors but should be treated with intravenous steroids and as per local institution guidelines. Baseline tests and parameters to monitor while on treatment are listed in Table 2, and Table 3 summarizes suggested dose modifications and management for irAEs according to CTCAE grading. Many of these recommendations are based on previous experience with CTLA-4 inhibitors, which have a similar spectrum of toxicity. When suspecting an irAE, other diagnoses should be excluded, such as infection and cancer progression. Management may require the input of the multidisciplinary team. As a general rule, patients with grade 1 irAEs rarely require corticosteroids. Grade 2 events should prompt initiation of treatment with topical or systemic steroids (0.5–1 mg/kg/day). If hospitalization is required or if a grade 3 irAE has occurred, patients should begin oral or intravenous (IV) steroids, 1–2 mg/kg/day, reducing to 1 mg/kg/day, followed by a slow oral steroid taper. Grade 4 irAEs should always be treated with IV corticosteroids and consideration given to admission to intensive care. Prolonged steroid use should prompt prescription of concurrent gastroprotection with proton pump inhibitors or histamine blockers and prophylactic oral antibiotics, as per institutional guidelines. Long courses of corticosteroids may predispose to opportunistic infections, and one case of *Aspergillus* pneumonia has been reported [25]. It should be noted that steroid treatment of irAEs does not appear to be associated with loss of efficacy of ICPIs, with durable responses seen in patients even after prolonged steroid courses [26–28].

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SPECIFIC irAEs

Diarrhea

Diarrhea occurs less frequently with PD-1 inhibitors than with CTLA-4 inhibitors such as ipilimumab. In previous trials of

Table 1. Toxicities of PD-1 inhibitors in phase III studies in lung cancer

Adverse event	Occurrence, n (%)					
	Checkmate 017 (n = 131)		Checkmate 057 (n = 287)		Keynote 010 (n = 682)	
	Any grade	Grades 3–5	Any grade	Grades 3–5	Any grade	Grades 3–5
Adrenal insufficiency	0	0	0	0	5 (1)	1 (<1)
Arthralgia	7 (5)	0	16 (6)	0	32 (5)	0
Asthenia	13 (10)	0	29 (10)	1 (<1)	39 (5)	3 (<1)
Colitis	1 (1)	1 (1)	2 (1)	1 (<1)	6 (<1)	4 (<1)
Decreased appetite	14 (11)	1 (<1)	30 (10)	0	79 (12)	4 (<1)
Diarrhea	10 (8)	0	22 (8)	2 (1)	46 (7)	2 (<1)
Fatigue	21 (16)	1 (<1)	46 (16)	3 (<1)	95 (14)	10 (1)
Hepatotoxicity ^a	2 (2)	0	27 (11)	4 (2)	65 (10)	8 (1)
Hyperthyroidism	0	0	4 (1)	0	32 (5)	1 (<1)
Hypophysitis	0	0	0	0	2 (<1)	2 (<1)
Hypothyroidism	5 (4)	0	19 (7)	0	56 (8)	0
Infusion reaction	1 (<1)	0	8 (3)	0	5 (<1)	0
Nausea	12 (9)	1 (<1)	34 (12)	2 (<1)	68 (10)	3 (<1)
Pneumonitis	6 (5)	1 (1)	8 (3)	3 (1)	26 (4)	12 (2)
Pruritis	5 (2)	0	24 (8)	0	57 (8)	0
Pyrexia	6 (5)	0	8 (3)	0	24 (4)	1 (<1)
Skin rash	12 (4)	0	27 (9)	1 (<1)	73 (11)	2 (<1)

Data are collated from supplemental appendices.

^aElevated transaminases (alanine aminotransferase and aspartate aminotransferase), elevated alkaline phosphatase, elevated g-glutamyl transferase, or hyperbilirubinemia.

Abbreviation: PD-1, programmed cell death protein-1.

Table 2. Recommended monitoring for patients on PD-1 inhibitors

Toxicity	Baseline testing	Suggested ongoing monitoring ^a
Endocrine	<ul style="list-style-type: none"> • TSH,T3, and T4 • No other baseline hormonal testing needed 	<ul style="list-style-type: none"> • TSH every 4–6 weeks (every other dose) • No routine monitoring of other hormones needed
Hepatotoxicity	<ul style="list-style-type: none"> • LFTs • Hepatitis B surface antigen (HBsAg) • Hepatitis B surface antibody (anti-HBs) • Hepatitis B core antibody (anti-HBc) • Anti-HCV 	<ul style="list-style-type: none"> • LFTs prior to each cycle
Pneumonitis	<ul style="list-style-type: none"> • Chest radiograph • High-resolution chest CT scan with and without injection of contrast 	<ul style="list-style-type: none"> • Chest imaging every 4–6 weeks (every other dose) • If symptoms, resting and exertion pulse oximetry and high-resolution chest CT scan (consider spirometry with measurement of carbon monoxide-diffusing capacity)

^aImmune-related adverse events' surveillance should be continued every 12 weeks up to 1 year after discontinuation of immunotherapy.

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; LFTs, liver function tests; PD-1, programmed cell death protein-1; TSH, thyroid-stimulating hormone.

ipilimumab in melanoma, diarrhea of any grade occurred in 37%, with nearly 7% developing grade 3 or 4 diarrhea and 5% grade 3 or higher colitis [29]. In lung cancer, 8% of patients treated with PD-1 inhibitors developed diarrhea of any grade; grade 3 diarrhea occurred in fewer than 1% [6–8]. The median time to gastrointestinal irAE onset related to nivolumab was reported in Checkmate 057 as 4.7 weeks (range 0.4–68.6) and in Checkmate 017 as 3.0 weeks (range 0.1–91.0). Immunomodulating medication was required in 23% and 18%, respectively. The median time to resolution was 1.5 weeks (range 0.1–86.4

or longer), and 1.7 weeks (0.1–31.0) in Checkmate 057 and 017, respectively. Early initiation of steroid treatment has been proven to decrease the incidence of serious gastrointestinal irAEs [30]. Other causes of diarrhea or colitis, including infections, must be ruled out, and empiric antibiotics are a consideration in patients who present with fever, leukocytosis, or both.

For grade 1 diarrhea, the ICPI can be continued with adequate oral hydration and loperamide [31]. For grade 2 symptoms, the ICPI should be held. Treatment again includes hydration, together with oral diphenoxylate hydrochloride and

Table 3. Dose modifications and management for specific immune-related adverse events

Toxicity	CTCAE grade (version 4.0)	Dosing, management, and follow-up
Diarrhea	1 (increase of <4 stools/day over baseline; mild increase in ostomy output)	No dose modification Adequate oral hydration, electrolyte replacement, and loperamide Closer monitoring for worsening symptoms
	2 (increase of 4–6 stools/day over baseline; moderate increase in ostomy output)	Hold checkpoint inhibitor. Adequate oral hydration, dietary modifications Start oral diphenoxylate hydrochloride and atropine sulfate QID (consider budesonide 9 mg OD). If colitis is suspected or if symptoms persist for 5–7 days or relapse, gastroenterology consult, endoscopy, and treatment with prednisone 0.5–1 mg/kg/day or equivalent
	3 (increase of ≥ 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output, limiting self-care ADL)	Discontinue checkpoint inhibitor permanently. Hospitalization, intravenous hydration with electrolyte replacement Methylprednisolone 1–2 mg/kg/day i.v. for 3 days, then prednisone 1–2 mg/kg/day or equivalent Taper steroids over 4 weeks or longer, or up to 6–8 weeks if diffuse and severe ulceration or bleeding.
	4 (life-threatening consequences; urgent intervention indicated)	If no improvement within 5–7 days or relapse, consider infliximab 5 mg/kg.
Endocrine toxicity	1–2 (asymptomatic, clinical or diagnostic toxicity observations only OR mildly symptomatic, limiting instrumental ADL)	All cases: Continue checkpoint inhibitor. Evaluate endocrine function (TSH, cortisol, ACTH, LH, FSH, prolactin, testosterone) as indicated. Subclinical hypothyroidism (TSH <10 mIU/L) does not need to be treated. Replace other hormones as needed. Hypophysitis: Consider radiographic pituitary imaging.
	3–4 (severe or life-threatening symptoms, interference with ADL, requiring urgent medical intervention)	All cases: Hold checkpoint inhibitor. Hospitalization. Consider endocrine consultation. Evaluate endocrine function (as grades 1–2) as indicated. Rule out other medical causes (e.g., sepsis). Initiate appropriate hormonal replacement therapy. Rechallenge with immunotherapy once symptoms have improved to grades 0–1 or are stable on hormonal replacement therapy could be considered. Hypophysitis: Radiographic pituitary gland imaging (e.g., MRI brain with and without contrast) Administer methylprednisolone 1–2 mg/kg/day i.v. or equivalent and taper over 1 month (continuation of physiologic doses of steroids required for adrenal insufficiency).
Hepatotoxicity	1 (AST/ALT ULN – $3 \times$ ULN or bilirubin ULN – $1.5 \times$ ULN)	No dose modification Monitor LFTs prior to next cycle.
	2 (AST/ALT > 3 – $5 \times$ ULN or bilirubin > 1.5 – $3 \times$ ULN)	Hold checkpoint inhibitor. Repeat LFTs every 3 days. If persists for ≥ 14 days, treat as grade 3. Consider hepatology consultation.
	3 (AST/ALT > 5 – $20 \times$ ULN or bilirubin > 3 – $10 \times$ ULN)	Discontinue checkpoint inhibitor. Repeat LFTs every 1–2 days. Methylprednisolone 1–2 mg/kg i.v. daily
	4 (AST/ALT $> 20 \times$ ULN or bilirubin $> 10 \times$ ULN)	Consult hepatology. If no improvement in 48 hours, consider additional immunosuppression with mycophenolate mofetil. Once improves to grade 2 or less, taper steroids orally over 4 weeks.

(continued)

Table 3. (continued)

Toxicity	CTCAE grade (version 4.0)	Dosing, management, and follow-up
Pneumonitis	1 (radiographic changes only)	Consider delay of checkpoint inhibitor. Consider pulmonary and infectious disease consults. Monitor every 2–3 days, and reimaging at least every 3 weeks. If worsens, treat as higher grade.
	2 (mild to moderate new symptoms)	Hold checkpoint inhibitor until resolution to grades 0–1. Pulmonary and infectious disease consults Consider bronchoscopy. Prednisone 1–2 mg/kg/day or intravenous equivalent Monitor daily and consider hospitalization. Reimage every 1–3 days. Taper steroids over ≥ 4 weeks. If no improvement after 2 weeks or worsening, treat as grades 3–4.
	3–4 (severe new symptoms, new or worsening hypoxia, life-threatening)	Permanently discontinue checkpoint inhibitor. Pulmonary and infectious disease consults Consider bronchoscopy. Methylprednisolone 2–4 mg/kg/day i.v. Hospitalization; consider intensive care unit. Prophylactic antibiotics Taper steroids over ≥ 6 weeks. If no improvement after 48 hours or worsening, add additional immunosuppression (infliximab, cyclophosphamide, intravenous immunoglobulin, or mycophenolate mofetil).
Skin	1 (rash covers $<10\%$ BSA)	No dose modification Topical corticosteroids (e.g., betamethasone 0.1% cream) Oral antipruritic agents (e.g., H-1 blockers: diphenhydramine, hydroxyzine)
	2 (rash covers 10%–30% BSA, limiting instrumental ADL)	Consider withholding checkpoint inhibitor. Topical corticosteroids Consider addition of low-dose steroids: prednisone 0.5–1.0 mg/kg/day or equivalent. If no improvement within a week, taper steroids over 1 month. If symptoms worsen, treat as grades 3–4.
	3–4 (rash covers $> 30\%$ BSA, limiting self-care ADL; severe/life-threatening symptoms, including Stevens-Johnson syndrome, toxic epidermal necrolysis, full-thickness dermal ulcerations, and ulcerative or bullous dermatitis)	If moderate: Hold checkpoint inhibitor. Consider dermatology consult and biopsy. Methylprednisolone 1–2 mg/kg/day or oral equivalent; continue until improvement to grades 0–1. Taper over at least a month. If rapid improvement, may consider reinitiation of immunotherapy on a case-by-case basis. If severe: Permanently discontinue checkpoint inhibitor. Consider hospitalization. If no improvement within 48–72 hours, consider additional immunosuppression (e.g., infliximab).

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CTCAE, common terminology criteria for adverse events; FSH, follicle-stimulating hormone; i.v., intravenously; LFTs, liver function tests; LH, luteinizing hormone; MRI, magnetic resonance imaging; OD, once daily; QID, four times daily; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

atropine sulfate four times per day. Budesonide 9 mg once per day should be considered. If diarrhea persists or colitis is suspected, that is, abdominal pain or bleeding per rectum, gastroenterology should be consulted and a sigmoidoscopy or colonoscopy with biopsies performed. Colitis is characterized macroscopically by mucosal edema, erythema, and erosions. At

this point, oral or IV corticosteroids, 0.5–1 mg/kg, should be initiated [31, 32]. For grade 3 or 4 symptoms, IV fluid hydration with electrolyte replacement should be started immediately, with IV methylprednisolone (1–2 mg/kg/day) for 3 days, followed by oral prednisone (1–2 mg/kg/day, or equivalent) with a slow taper over at least 4 weeks. In patients with diffuse and

severe ulceration or bleeding, a taper of 6–8 weeks may be safer [33, 34]. If there is no improvement within 5–7 days, or relapse occurs, a single dose of infliximab (monoclonal antibody against tumor necrosis factor- α) (5 mg/kg) can be given, unless contraindicated. Another dose after 2 weeks may be required. For patients with concomitant hepatitis, mycophenolate mofetil should be used instead [32, 35].

Hepatic Toxicity

Immune-mediated hepatitis is an uncommon but potentially serious toxicity of PD-1 inhibitors, occurring in up to 11% of lung cancer patients on PD-1 axis inhibitor trials. It is most commonly observed as an asymptomatic elevation in serum transaminases (alanine aminotransferase and aspartate aminotransferase), but hyperbilirubinemia has also been reported. Fever has also been observed, and in severe hepatitis, symptoms such as malaise or nausea can develop. Although pathologic changes similar to acute viral or autoimmune hepatitis have been reported on liver biopsies of patients treated with ipilimumab, this has not yet been confirmed with PD-1 inhibitors [36]. Hepatic serious adverse events with nivolumab are rare: two (1%) were reported in Checkmate 057 and none in Checkmate 017. For pembrolizumab (Keynote 010), three cases of autoimmune hepatitis (<1% of treated patients) were recorded. The median time to hepatic irAE onset related to nivolumab was reported in Checkmate 057 as 5.1 weeks (range 0.1–37.4) and in Checkmate 017 as 17.6 weeks (range 4.1–31.1). In Checkmate 057, 2 of 15 patients required immune-modulating medication; neither of the 2 affected patients required this in Checkmate 017. The median time to resolution in Checkmate 057 was 2.1 weeks (range 0.1–69); in Checkmate 017, 1 patient had resolution within 3 weeks, whereas the other had ongoing toxicity at 22 weeks. These events were generally reversible, with most patients being able to resume treatment after a delay; only 1 patient on Checkmate 057 permanently discontinued nivolumab because of hepatotoxicity.

PD-1 inhibitors should be used with caution in patients with significant liver disease or elevated serum transaminases. Liver enzymes should be assessed at baseline and prior to each cycle. Patients who develop grade 2–4 toxicity should undergo investigations to rule out other causes: liver ultrasound, viral screening, review of concomitant medications, and hepatology consultation with consideration of liver biopsy. Institution of corticosteroids has been associated with improvement in liver biochemistry in patients with grade 3–4 (or persistent grade 2) dysfunction. In refractory cases, additional immunosuppression with mycophenolate mofetil is recommended. Infliximab is not recommended because of potential hepatotoxicity.

Pancreatic Toxicity

The most common pancreatic toxicity of PD-1 inhibitors is an asymptomatic elevation of lipase or amylase. In the Keynote 010 trial, pancreatitis was reported at any grade in three patients and at grades 3–5 in two. One patient in the Checkmate 017 study had grade 3–4 elevated lipase, and no elevation in amylase or lipase was reported in the Checkmate 057 study. It appears that clinically significant pancreatitis is rare. Nonetheless, clinical signs or symptoms of pancreatitis warrant investigation with amylase and lipase measurement, followed by imaging studies as appropriate. Routine monitoring of amylase/

lipase is not recommended, and treatment should not be withheld for minor asymptomatic elevations in these parameters.

Pneumonitis

Immune-related pneumonitis, which is defined as a focal or diffuse inflammation of the lung parenchyma, is one of the few potentially life-threatening irAEs. It occurs more commonly in patients with lung cancer than with other malignancies [37]. Prior thoracic radiotherapy and preexisting chronic lung disease—especially interstitial lung disease, asthma, and chronic obstructive pulmonary disease—may increase the risk [38]. It is a diagnosis of exclusion, when active infection and malignant lung infiltration have been ruled out. Patients may present with new onset or worsening shortness of breath, cough, chest pain, or fever, and fine inspiratory crackles on lung auscultation. Chest imaging will typically show ground-glass opacities or patchy nodular infiltrates, predominantly in the lower lobes. Radiological abnormalities can be variable but are often focal and very different from the diffuse pneumonitis associated with targeted agents such as tyrosine kinase inhibitors (Figure 1). A review of 653 patients with various cancers who received an anti-PD-1/PD-L1 monoclonal antibody, either alone or in combination, found 36 cases (6%) of pneumonitis [37]. Five distinct radiologic subtypes were identified: cryptogenic obstructive pneumonia (COP)-like, ground-glass opacities, hypersensitivity type, interstitial type, and pneumonitis not otherwise specified. Radiologic subtypes of pneumonitis were associated with primary disease site, and patients with lung cancer tended to develop COP-like pneumonitis, the subtype that seemed to be the most clinically aggressive. In Checkmate 017 and Checkmate 057, there was a wide range in time to onset, with medians of 15.1 weeks (2.6–85.1) and 31.1 weeks (11.7–56.9), respectively. Median times to resolution were 5.0 and 5.7 weeks. In Keynote 010, there were three deaths from pneumonitis attributed to treatment, two in the pembrolizumab 2 mg/kg group and one in the pembrolizumab 10 mg/kg arm.

For grade 1 pneumonitis in asymptomatic patients, delay of ICPI should be considered, and patients must be monitored every 2–3 days for development of symptoms. For symptomatic patients, steroids are the mainstay of treatment, with prednisone 1–2 mg/kg/day or IV equivalent for grade 2, and methylprednisolone 2–4 mg/kg/day or IV equivalent for grades 3–4, along with empiric antibiotics until infection is excluded. For grade 2, the ICPI should be held until resolution to grade 1 or less, then carefully reintroduced. In one review, five patients with grade 1 pneumonitis, for which immunotherapy was delayed, have been rechallenged, and no recurrence was observed [39]. These data have not been reported for grade 2 pneumonitis. For grades 3–4, the drug should be permanently discontinued. Pulmonary and infectious disease consults should be considered for grade 1 pneumonitis and are recommended for grades 2–4. Bronchoscopy with bronchoalveolar lavage and tissue biopsies to investigate for pulmonary infection or progressive malignancy should also be considered for grades 2–4.

Endocrine Disorders

Autoimmune endocrinopathies, one of the hallmark irAEs, occur less frequently with PD-1 inhibitors than with CTLA-4 inhibitors. Thyroid dysfunction is most common, occurring in 4%–7% of patients [6, 7, 40]. In Checkmate 017 and 057, median time to onset was 7 weeks and 12 weeks, respectively,

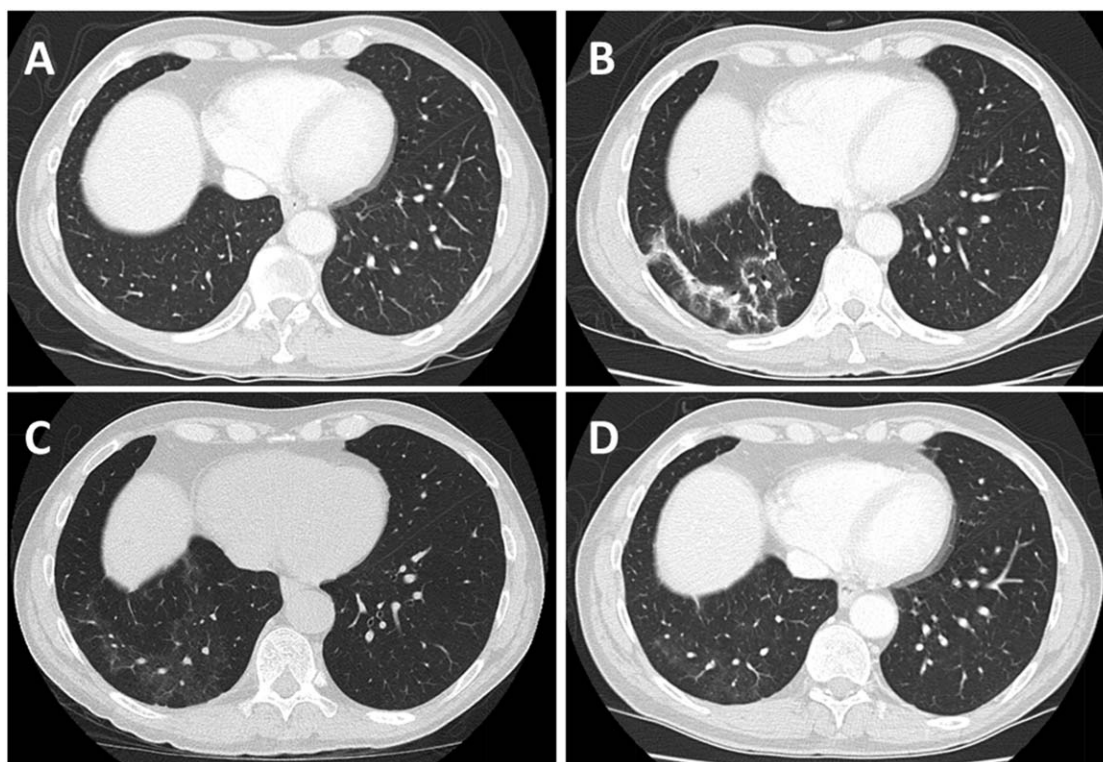


Figure 1. Pneumonitis. Chest computed tomography scans of a 72-year-old male with stage IV lung adenocarcinoma on second-line nivolumab. **(A):** After three cycles. **(B):** Grade 1 cryptogenic organizing pneumonia-like pneumonitis after eight cycles. **(C):** Improvement after 4 weeks of steroids and holding nivolumab; then steroids were tapered slowly over 4 more weeks, and nivolumab was restarted. **(D):** After 10 cycles.

although the range varied widely (0.4 to 47 or more weeks). Time to resolution also varied from 2.5 to 12.1 weeks [6, 7, 28]. The mechanism of hypothyroidism is similar to autoimmune thyroiditis, with immune-mediated destruction of thyroid tissue causing a temporary, often subclinical hyperthyroidism, followed by a permanent hypothyroidism in most cases. Abnormalities are usually detected on screening tests, although classic symptoms such as fatigue, loss of appetite, bradycardia, and others can be seen. Diagnosis can be confirmed by detection of antithyroglobulin and antithyroid peroxidase antibodies [41]. Treatment involves replacement of thyroid hormone, and the PD-1 inhibitor may be continued. Treatment of subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 4 to 10 mIU/L) is generally not needed, given the limited life expectancy of this population, similar to guidelines on elderly patients [42]. Beta blockers can be used to treat temporary hyperthyroidism, with consideration given to a short course of steroids (e.g., 1 mg/kg prednisone). TSH, T3, and T4 are recommended at baseline, with monitoring of TSH every second cycle [43].

Hypophysitis is rare and has been reported once in trials (Keynote 010) [8]. Symptoms—such as asthenia, headaches, vertigo, and diplopia—can be due to the decrease in pituitary hormones, as well as mass effect from gland destruction and edema. Adrenal, thyroid, and gonadal functions are most commonly affected, although prolactin, growth hormone, and posterior pituitary deficits have been seen in some case reports [41]. For severe and symptomatic hypophysitis, the PD-1 inhibitor should be initially held. Treatment consists of appropriate hormonal replacement. Brain magnetic resonance imaging

(MRI) should be performed to investigate for alternative diagnoses but in hypophysitis may show pituitary mass effect and edema. High-dose glucocorticoids should be commenced as IV methylprednisolone 1–2 mg/kg/day for 3–5 days, followed by oral prednisone 1–2 mg/kg/day, with tapering over 4 weeks to physiological doses [41]. Small studies have shown that 37%–50% of gonadal and thyroidal deficiencies related to hypophysitis can recover, but adrenal insufficiency is usually permanent [44]. Once hormonal levels are stable and symptoms have resolved, PD-1 inhibitors have been safely reinitiated in the past. Rechallenge could be considered on an individualized basis [41, 45, 46].

Primary adrenocortical insufficiency has also been reported (<1%) with pembrolizumab [8] and is treated with glucocorticoid replacement at physiological doses. Adrenal crisis, as always, requires hospitalization, endocrine consultation, IV corticosteroids, and aggressive fluid and electrolyte replacement. Immunotherapy should again be held in these cases with reinitiation once hormone levels are stable. With the very low rate of nonthyroid endocrinopathies with PD-1 inhibitors in comparison with the CTLA-4 inhibitors, routine measurement of hormonal markers outside of thyroid testing is not recommended [2].

Skin Toxicity

Skin irAEs can be seen with PD-1 inhibitors and manifest as a maculopapular rash on the trunk and extremities with pruritus, but reticular, erythematous, and lichenoid rashes have also been seen [35, 47]. Severe toxicities such as toxic epidermal necrolysis and bullous dermatitis have also been documented

in case reports [48, 49]. All of these toxicities have been reported less frequently in the NSCLC data in comparison with the melanoma trials. [50] In Checkmate 017, Checkmate 057, and Keynote 010, rash or pruritis was seen in up to 11% of patients. Grade 3–4 skin toxicities requiring discontinuation were rare, occurring in only one patient in each Checkmate trial and one in each dose level of Keynote 010. Median onset has been seen at 5–7 weeks, although the range is quite variable (0.1–66.1 weeks) [6–8].

Grades 1 and 2 toxicities can be managed with emollients, topical steroid creams (e.g., betamethasone 0.1%), and oral antipruritic agents (e.g., H-1 blockers). Interruption of the PD-1 inhibitor is generally unnecessary. For grade 2 toxicities that persist for >1 week or are symptomatic, the PD-1 inhibitor can be held, and systemic corticosteroids may be considered (prednisone 0.5–1 mg/kg/day until improvement to grade 1 or less, followed by a taper over 1 month). The PD-1 inhibitor can be restarted once the rash improves to grade 1 or less. Grade 3–4 rash should prompt discontinuation of the drug and hospitalization. Systemic corticosteroids (methylprednisolone IV 1–2 mg/kg/day or oral equivalent) should be initiated and a dermatology consult considered. Once there is improvement to grade 1 or less toxicity, steroids can be tapered for 1 month. Reinitiation of immunotherapy is generally not recommended unless a rapid improvement has occurred. Skin biopsy may be required if full thickness dermal ulceration, blistering, or bullous, necrotic, or hemorrhagic changes are seen, and these patients should not be rechallenged with ICPIs.

Neurologic Disorders

There have been relatively few incidences of patients developing neurological irAEs with single-agent PD-1 inhibitors. Isolated cases of encephalitis [7] and a myasthenia-like syndrome [6] have been reported. One patient also experienced a cerebrovascular event [7] and another cerebral vasculitis; the cerebral vasculitis was successfully treated with aspirin [51]. Guillain-Barre syndrome has been reported with ipilimumab [52, 53]. Given the ongoing combination trials of CTLA-4 inhibitors and PD-1 inhibitors, physicians should remain vigilant to this potentially fatal irAE. Neurological irAEs are usually serious; management involves IV systemic corticosteroids and consultation with a neurologist. No specific surveillance is recommended for neurologic disorders beyond standard physical examination at clinic visits.

Increasing data suggest that ICPIs can also target brain metastases with durable responses reported [54–56]. It is not yet known if and when radiation should be combined with the ICPI in this patient cohort. One study has documented improved survival when ipilimumab was combined with stereotactic radiosurgery (SRS) versus SRS alone in metastatic melanoma [57]. Radiation necrosis is, however, thought to occur with an increased frequency when immunotherapy is used [58]. Pseudoprogression remains a challenge, as highlighted by case reports in which necrotic tissue and scattered tumor cells with inflammatory cells have been found at surgical resection [59, 60]. Treatment options include surgery and steroids; bevacizumab has been reported to improve radiation necrosis [61]; however, its role in this setting is unknown.

AGENTS IN DEVELOPMENT

Several promising agents targeting PD-1/PD-L1 are in clinical development. At present, there are limited datasets regarding their toxicity profiles, but available reports point to similar issues as those seen with nivolumab and pembrolizumab, and these are summarized in Table 4.

Several promising agents targeting PD-1/PD-L1 are in clinical development. At present, there are limited datasets regarding their toxicity profiles, but available reports point to similar issues as those seen with nivolumab and pembrolizumab.

Atezolizumab (formerly MPDL3280A) is a PD-L1 inhibitor that has been the subject of completed phase II studies in advanced NSCLC. The BIRCH study reported treatment-related AEs in 64%; these were grades 3–4 in 11% [62]. The most common treatment-related AEs were fatigue (80% any grade), diarrhea (10% any grade), and nausea (10% any grade). Other AEs of interest were rash (9% any grade), hypothyroidism, pneumonitis (grades 3–4 in 1.5%; 1 patient had grade 5 pneumonitis), and elevation of transaminases. In the POPLAR study, treatment-related AEs were reported in 67% and were grades 3–4 in 12%. Elevated transaminases (any grade) were seen in 4%, pneumonitis in 2%, and colitis and hepatitis in 1% each [63]. Phase III studies are in progress.

Avelumab (MSB0010718C) is an anti-PD-L1 antibody that has reported activity in a phase I expansion cohort of 184 patients with advanced NSCLC [64, 65]. Treatment-emergent adverse events (TEAEs) occurred in 142 patients (77%), with the most common reported toxicities being fatigue in 25% and infusion reaction in 21%. The high rate of infusion reactions has prompted the implementation of a premedication regimen for this agent. Other irAEs included hypothyroidism in 6% and adrenal insufficiency in 1%. TEAEs leading to death occurred in 2 patients: 1 with radiation pneumonitis and 1 with acute respiratory failure.

Durvalumab (formerly MEDI4736) is another anti-PD-L1 antibody currently in development. A dose expansion study has been completed with 228 patients with advanced NSCLC and reported drug-related events in 50%, with grade 3–4 AEs in 8% and AEs leading to discontinuation in 5% [66]. Rash (8%) and diarrhea (7%) were the most common reported drug-related AEs, with pruritus, elevated transaminases, and thyroid disorders also noted.

Combinations of PD-/PD-L1 and CTLA-4 antibodies are also in development. In a phase Ib study of durvalumab and tremelimumab in advanced NSCLC, treatment-related AEs were observed in 80% of patients, with 42% grade 3–4 events and three treatment-related deaths [67]. Corticosteroids were required in 50%, and 28% discontinued treatment. The most common events were fatigue, dyspnea, nausea, diarrhea, colitis, and rash. The combination of nivolumab and ipilimumab has also been the subject of a phase I study and reported treatment-related AEs in 77% of patients, with 29% experiencing a grade 3–4 event. Thirteen percent of patients

Table 4. Selected adverse events in early studies of PD-L1 inhibitors (and in combination with CTLA-4 inhibitors) in non-small cell lung cancer

Adverse event	Occurrence, n (%)						
	Atezolizumab ^a (POPLAR)	Avelumab ^b (JAVELIN)		Durvalumab (1108 study)		Durvalumab, 10–20 mg/kg, tremelimumab, 1 mg/kg	
	(n = 131)	(n = 184)		(n = 228)		(n = 56)	
	Any grade	Any grade	Grades 3–4	Any grade	Grades 3–4	Any grade	Grades 3–5
Adrenal insufficiency	—	2 (1)	—	1 (<1)	0	—	—
Amylase increased	—	—	—	—	—	11 (20)	1 (2)
Arthralgia	—	—	—	—	—	6 (11)	0
Asthenia	9 (6)	—	—	—	—	4 (7)	1 (2)
Autoimmune hepatitis	—	—	—	1 (<1)	1 (<1)	—	—
Colitis	—	—	—	—	—	2 (4)	1 (2)
Decreased appetite	—	13 (7)	—	—	—	12 (21)	1 (2)
Diarrhea	10 (7)	13 (7)	0	15 (7)	1 (<1)	18 (32)	4 (7)
Dyspnea	—	3 (2)	2 (1)	—	—	9 (16)	3 (5)
Fatigue	29 (20)	46 (25)	0	—	—	21 (38)	2 (4)
Hepatotoxicity ^c	3 (2)	—	—	7 (3)	1 (<1) ^d	7 (11) ^d	1 (2)
Hyperthyroidism	—	—	—	9 (4)	1 (<1)	—	—
Hypophysitis	—	—	—	—	—	1 (2)	1 (2)
Hypothyroidism	5 (4)	11 (6)	0	8 (4)	0	6 (11)	1 (2)
Infusion reaction	—	38 (21)	4 (2)	1 (<1)	0	—	—
Lipase increased	—	1 (<1)	3 (2)	—	—	10 (18)	5 (9)
Nausea	17 (12)	24 (13)	0	—	—	15 (27)	0
Pneumonitis	—	—	—	3 (1)	0	0	0
Pruritus	—	—	—	10 (4)	0	13 (23)	0
Pyrexia	—	—	—	—	—	10 (18)	0
Skin rash	—	—	—	17 (8)	0	12 (21)	0

^aOnly related adverse events occurring in ≥10% of patients were reported.

^bTreatment-emergent adverse events (TEAEs) occurring in ≥5% of patients, and grade 3–4 TEAEs occurring in ≥1%, were reported.

^cElevated transaminases (ALT and AST), elevated alkaline phosphatase, elevated GGT, or hyperbilirubinemia.

^dFigures for ALT, which represented most frequent liver toxicity. Grade 3 elevations in AST and GGT occurred in four patients.

Abbreviations: —, not reported; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTLA-4, cytotoxic T-lymphocyte associated antigen 4; GGT, γ-glutamyl transferase; PD-L1, programmed death ligand-1.

discontinued treatment because of AEs; the most common toxicities involved skin, endocrinopathies, hepatic disorders, and pulmonary disorders [68]. Overall, the combination of PD-1/PD-L1 and CTLA-4 antibodies appears to increase toxicity more than PD-1/PD-L1 blockade alone in patients with advanced NSCLC, but the efficacy results are promising, and further study is required of all these agents and combinations.

SUMMARY

The PD-1/PD-L1 inhibitors are part of a new wave of immunotherapy treatments for cancer. Although these new agents are generally more tolerable than conventional cytotoxic chemotherapy, their irAEs are unique and can be quite serious, especially if they are not recognized and treated appropriately. Monitoring and management guidelines, such as the ones provided here, are an essential first step in dealing with this new era of treatment. Close coordination and partnership with other medical subspecialties is a necessity in dealing with these

new organ-specific toxicities. Many questions are still left unanswered; new PD-1/PD-L1 inhibitors, combinations of immunotherapy agents, and the addition of immunotherapy to cytotoxic chemotherapy, radiation, or targeted agents are currently under study. Management of these toxicities may have to change with these new therapeutic options, and we must be aware of the possibility of new challenges related to these advancements.

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DISCLOSURES

The authors indicated no financial relationships.

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